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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [6] :
C07D 401/12

A1

(11) International Publication Number: WO 99/47514

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/EP99/01574

(22) International Filing Date: 11 March 1999 (11.03.99)

(30) Priority Data:
9805558.5 17 March 1998 (17.03.98) GB

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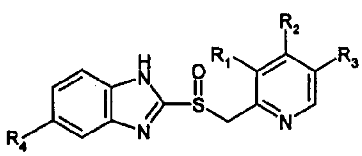
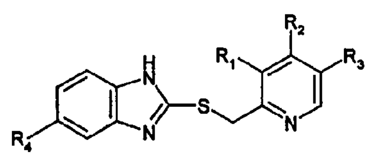
(81) Designated States: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CHEMICAL PROCESS FOR THE PRODUCTION OF SULPHINYL DERIVATIVES BY OXIDATION OF THE CORRESPONDING CO-DERIVATIVES WITH PERBORATES



(I)



(II)

(57) Abstract

A process for the preparation of a compound of formula (I) in which R_1, R_2, R_3 and R_4 represent: a) (R_1=CH_3; R_2=OCH_3; R_3=CH_3; R_4=OCH_3) or b) (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) or c) (R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) respectively and pharmaceutically acceptable salts thereof, comprising reacting a compound of formula (II) in which R_1, R_2, R_3 and R_4 represent a) (R_1=CH_3; R_2=OCH_3; R_3=CH_3, R_4=OCH_3) or b) (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) or c) R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) respectively, with a perborate salt in a liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0 °C to the boiling point of the liquid diluent employed.

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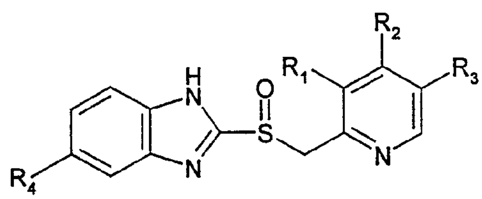
CHEMICAL PROCESS FOR THE PRODUCTION OF SULPHINYL DERIVATIVES BY OXIDATION OF THE CORRESPONDING THIO-DERIVATIVES WITH PERBORATES

The present invention describes an improved process for the preparation of substituted 2-(2-pyridylmethyl)sulphinyl-1*H*-benzimidazoles particularly omeprazole, lansoprazole and pantoprazole by oxidising the corresponding substituted 2-(2-pyridylmethylthio)-1*H*-benzimidazole.

Several proton-pump inhibitors, which are useful in the treatment of duodenal ulcers, of formula A are known. These include omeprazole (R_1=CH_3; R_2=OCH_3; R_3=CH_3; R_4=OCH_3) which is described in EP5129, lansoprazole (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) which is described in EP174,726 and pantoprazole (R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) which is described in EP166,287.

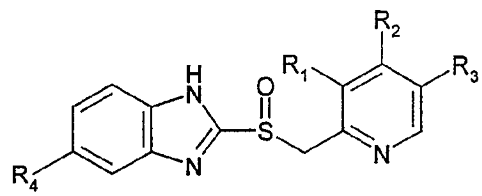


A

Many methods for preparing such compounds by the oxidation of the corresponding 2-(2-pyridylmethylthio)-1*H*-benzimidazole have been described. Examples of the oxidising agents used are 3-chloroperoxybenzoic acid (WO91/18895, EP533752, US5,386,032, ES43816 and EP484265), magnesium monoperoxyphthalate (EP533264 and US5,391,752), ammonium molybdate (EP484,265), iodosobenzene (ES539793), methyliodosobenzene (ES540147), sodium periodate (ES550070) and vanadium oxide (EP302720).

However, there remains a need for a cheap and efficient process for oxidising 2-(2-pyridylmethylthio)-1*H*-benzimidazoles which is reliable, produces waste streams which are easily disposed of without causing harm to the environment and produces a stable final product.

The present invention provides a process for the preparation of a compound of formula I



I

in which R_1, R_2, R_3 and R_4 represent

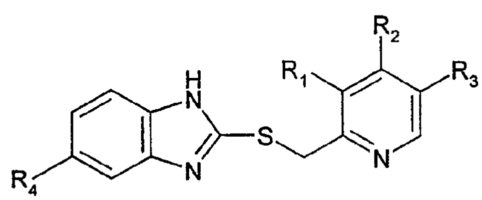
a) (R_1=CH_3; R_2=OCH_3; R_3=CH_3; R_4=OCH_3) or

b) (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) or

c) (R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) respectively

and pharmaceutically acceptable salts thereof

comprising reacting a compound of formula II



II

in which R_1, R_2, R_3 and R_4 represent

a) (R_1=CH_3; R_2=OCH_3; R_3=CH_3; R_4=OCH_3) or

b) (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) or

c) (R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) respectively

with a perborate salt in a liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the liquid diluent employed.

Suitably the perborate salt is a metallic perborate salt or an ammonium perborate salt. The perborate salt may be anhydrous or hydrated. Preferably the perborate salt is potassium or sodium perborate. More preferably the perborate salt is sodium perborate. Most preferably the perborate salt is sodium perborate monohydrate or sodium perborate tetrahydrate.

Suitably the amount of perborate salt employed in the process is in the range of 0.8 to 3 moles per mole of the compound of formula II employed in the process.

Preferably the amount of perborate employed is in the range 0.95-2.0 moles per mole of the compound of formula II employed in the process. More preferably the amount of perborate employed is in the range 1.0-1.9 moles per mole of the compound of formula II employed in the process for example 1.1-1.5 moles per mole of the compound of formula II. Most preferably the amount of perborate employed is in the range 1.4-1.8 moles per mole of the compound of formula II employed in the process.

The purpose of the liquid diluent is to allow contact between the compound of formula II and the perborate salt at the required temperature. Any liquid diluent, which is inert to the reactants, in which this purpose is achieved may be used.

Preferably the liquid diluent is selected from water, a C_{1-4} alcohol, toluene, tetrahydrofuran, acetone, a C_{2-6} diol, a C_{3-6} triol, ethyl acetate or mixtures thereof. More preferably the liquid diluent is a water/alcohol mixture, for example a water/methanol or a water/ethanol mixture. Most preferably the diluent is a water/methanol mixture optionally containing toluene.

Preferably the process is carried out at a pH in the range of 8.5 to 12. More preferably 10 to 12. Most preferably the process is carried out at a pH in the range of 10 to 11.

Suitably the pH of the process is controlled by the addition of a base for example an alkali metal hydroxide an alkali metal carbonate, an alkali metal bicarbonate or an amine e.g. ammonia or an organic amine or mixtures thereof. Preferably the base is sodium hydroxide.

It will be appreciated by those skilled in the art that when the reaction is carried out at high pH a salt of the desired product may be obtained. Lowering the pH of the reaction mixture, for example by addition of an acid or preferably of a less basic base, allows the isolation of the compound of formula I as the free heterocycle.

Preferably the process is carried out at a temperature in the range of 0 to 150°C and more preferably in the range of 15 to 115°C. Most preferably the process

is carried out at a temperature in the range of 40 to 55°C, particularly at a temperature in the range of 45 to 50°C.

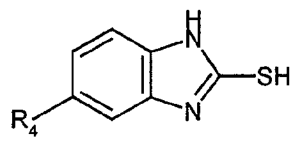
The process of the present invention has several advantages over previously described oxidation processes. The reagents employed are cheap, non-hazardous and environmentally friendly, for example sodium perborate is used in domestic washing powder, in mouth washes and in cleaning fluids for contact lenses. Sodium perborate has exceptional storage stability and is not shock sensitive. The process gives good yields reproducibly and provides a product of high purity which is chemically more stable than the products of other oxidation processes especially those carried out in acidic conditions. In addition environmentally friendly liquid diluents may be used.

The process of the present invention has two further advantages over the prior art processes. Firstly, this process step may be combined with the previous process step and thus avoid isolation of the compound of formula II. This leads to cost reduction in the process through improved processing times. Secondly, in comparative experiments sodium perborate appears to give fewer impurities arising from over-oxidation, for example formation of a sulphone, or an *N*-oxide, or a sulphone *N*-oxide, than previously known oxidants, for example 3-chloroperoxybenzoic acid.

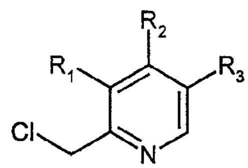
The desired product can be isolated from the reaction mixture and purified by conventional means e.g. extraction and recrystallisation or filtration followed optionally by recrystallisation.

In a preferred process of the present invention a compound of formula IIa is reacted with sodium perborate in a mixture of water and methanol at a pH in the range of 8.5 to 10 at a temperature in the range of 15 -115°C to give a compound of formula Ia (omeprazole).

In a more preferred process of the present invention the compound of formula II is prepared by reacting a compound of formula III


III

or a salt thereof in which R_4 is as previously defined with a compound of formula IV


IV

or a salt thereof in which R_1, R_2, and R_3 are as previously defined, in a second liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the second liquid diluent employed and is then reacted with a perborate salt without isolation.

The purpose of the second liquid diluent is to allow contact between the compound of formula III and the compound of formula IV at the required temperature. Any liquid diluent, which is inert to the reactants, in which this purpose is achieved may be used. Preferably the reaction of III and IV is carried out at a temperature in the range of 10-100°C, preferably at a temperature in the range of 20-80°C and more preferably at a temperature in the range of 40-60°C.

Preferably the second liquid diluent is selected from water, a C_{1-4} alcohol, toluene, tetrahydrofuran, acetone, a C_{2-6} diol, a C_{3-6} triol, ethyl acetate or mixtures thereof. More preferably the second liquid diluent is a water/alcohol mixture, for example a water/methanol or a water/ethanol mixture. Most preferably the diluent is a water/methanol mixture optionally containing toluene. Especially preferably the second liquid diluent is the same as the first liquid diluent. This avoids further processing for example diluent exchange.

In a preferred embodiment the compound of formula III is present as the free thiol, initially, and the process is carried out in the presence of a base. Preferably the base is an alkali metal hydroxide for example sodium hydroxide or potassium hydroxide. More preferably the base is sodium hydroxide.

In a preferred embodiment the compound of formula IV is present as a salt and sufficient base is used in the process to neutralise the salt of the compound of formula IV and to form a salt of the compound of formula III. Preferably the salt of the compound of formula IV is the hydrochloride salt, the hydrobromide salt, the acetate salt, the nitrate salt or a salt of sulphuric acid or the salt of a phosphoric acid. Most preferably the salt is the hydrochloride salt.

Preferably the amount of base employed is in the range of 2.0 to 5.0 moles per mole of the compound of formula III. More preferably the amount of base employed is in the range of 3 to 4 moles per mole of the compound of formula III.

In a preferred embodiment of the process a purification solvent is added at the end of the oxidation reaction. The purification solvent has been found to remove certain impurities from the crude reaction product by dissolving these impurities so that on filtration the product obtained requires fewer recrystallisations than would otherwise be necessary. This provides time and energy and therefore cost savings in the process. The purification solvent also aids the filtration process by changing the physical nature of the product so that it can be more readily filtered. Preferably the purification solvent is immiscible with the liquid diluent.

Preferred purification solvents are hydrocarbons, including aliphatic and aromatic hydrocarbons, and ethers, particularly di(C_{1-6}alkyl) ethers in which the alkyl groups are the same or different, and esters, for example ethyl acetate and mixtures thereof. More preferably the purification solvent is *tert*-butyl methyl ether, diisopropyl ether, hexane , heptane or toluene and mixtures thereof. Most preferably the purification solvent is *tert*-butyl methyl ether, diisopropyl ether or hexane and mixtures thereof. Especially preferably the purification solvent is *tert*-butyl methyl ether or diisopropyl ether.

The invention is illustrated by the following Examples which are given by way of example only. The final product of each of these Examples was characterised by one or more of the following procedures: high performance liquid chromatography; elemental analysis, nuclear magnetic resonance spectroscopy, infrared spectroscopy and high resolution mass spectroscopy. The compounds of formula II, III and IV used in the Examples were either commercially available or were prepared by the methods given in EP5129, EP174,726 or EP166,287 which are incorporated herein by reference.

Example 1

A solution of sodium hydroxide pellets (0.32 g), sodium perborate tetrahydrate (1.43 g) and water (35 ml) was prepared by stirring and heating the mixed components until a solution was obtained, and was then added dropwise with stirring over 2.5 hours to a solution of 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]thio}-1*H*-benzimidazole (2.0 g) in methanol (20 ml) and toluene (2 ml) which was boiling under reflux. The methanol was removed under reduced pressure and the residue was cooled to 50°C and then added to saturated sodium bicarbonate solution (20 ml). The mixture was extracted with dichloromethane (2 x 10 ml), the combined extracts were dried, filtered and evaporated to give 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphinyl}-1*H*-benzimidazole (1.60 g). Yield 86.5%.

Example 2

A solution was prepared by dissolving sodium hydroxide pellets (17.7 g) and sodium perborate tetrahydrate (68.3 g) in water (1085 ml) with stirring and heating and this solution was then added dropwise to a solution of 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]thio}-1*H*-benzimidazole (83.4 g) in methanol (834 ml) whilst the mixture was boiled under reflux. The methanol was removed under reduced pressure and the residue was cooled to 50°C and then added to saturated sodium bicarbonate solution (830 ml). The mixture was cooled to 30°C and extracted with dichloromethane (2 x 400 ml). The combined dichloromethane extracts were dried over magnesium sulphate, filtered and

evaporated to give give 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphinyl}-1*H*-benzimidazole (74.0 g, 84.6% yield). This material was stirred in ethyl acetate (222 ml) for 1 hour then filtered. The residue was washed with ethyl acetate (2 x 25 ml) and dried to give a product which was 96.7% pure by HPLC.

Example 3

A solution of sodium hydroxide (1.0 g) and sodium perborate tetrahydrate (3.8 g) in water (65.0 ml) was prepared by heating and stirring. This solution was then added dropwise to a solution of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-ylmethylthio]-1*H*-benzimidazole (5.0 g) in methanol (50.0 ml) which was being boiled over 2 hours at reflux with stirring. The mixture was stirred and boiled for a further 15 minutes, then the methanol and water were removed under reduced pressure to give a residue which was cooled to 50°C and added to saturated sodium bicarbonate solution (50.0 ml). This mixture was cooled to 30°C and then extracted with dichloromethane (2 x 25 ml). The combined extracts were dried, filtered and evaporated to give 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinylmethylsulphinyl]-1*H*-benzimidazole (4.8 g, 92.3% yield). The purity of this material was 90.3% by HPLC. This solid was stirred with ethyl acetate (14.4 ml) for 1 hour and then the solid collected by filtration, washed with ethyl acetate and dried to give material which was 91.4% pure by HPLC.

Example 4

A solution of sodium hydroxide (9.8 g) and sodium perborate tetrahydrate (37.3 g) in water (638.3 g) was prepared by heating and stirring. This solution was then added dropwise over 2.5 hours to a solution of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-ylmethylthio]-1*H*-benzimidazole (49.1 g) in methanol (491.0 ml) which was being boiled at reflux with stirring. The mixture was stirred and boiled for a further 15 minutes, then the methanol and water were removed under reduced pressure to give a residue which was cooled to 50°C and added to saturated sodium bicarbonate solution (491 ml). This mixture was cooled to 30°C and then extracted with dichloromethane (2 x 245.5 ml). The combined extracts

were dried, filtered and evaporated to give 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinylmethylsulphinyl]-1*H*-benzimidazole in quantitative yield.

Example 5

In a similar manner to Example 1, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methylthio]-1*H*-benzimidazole is reacted with sodium perborate to give 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1*H*-benzimidazole.

Example 6

A mixture of 5-methoxy-2-mercapto-1H-benzimidazole (198.8 g), methanol (380 ml) and water (760 ml) was stirred while sodium hydroxide solution (215 ml, 46-48% w/w) was added over 5 minutes. The mixture was stirred at 45-50°C and a solution of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (245 g) in water (1136 ml) was added over 1 hour. The mixture was stirred at 45-50°C for 2 hours and then sodium perborate tetrahydrate (202.4 g) was added. The mixture was stirred at 45-50°C for 18 hours. Further sodium perborate tetrahydrate (16 g) was added and the mixture was stirred for a further 4 hours. The mixture was cooled to 30-35°C and sodium hydrogen carbonate (221.9 g) was added followed by water (763.4 ml) and *tert*-butyl methyl ether (763.4 ml). The mixture was stirred vigorously for 2 hours then filtered to give a product which was washed with *tert*-butyl methyl ether (500 ml) and then dried under vacuum at 45-50°C for 21 hours to give 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphinyl}-1*H*-benzimidazole (293.4 g, 77% yield, purity by HPLC 98.3%).

Example 7

A mixture of 5-methoxy-2-mercapto-1H-benzimidazole (4.3 g), methanol (8.4 ml) and water (16.7 ml) was stirred while sodium hydroxide solution (4.7 ml, 46-48% w/w) was added over 5 minutes. The mixture was stirred at 45-50°C and a solution of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (5.3 g) in water (25 ml) was added over 35 minutes at 45-50°C. The mixture was stirred at 45-50°C for 1.75 hours and then sodium perborate tetrahydrate (4.5 g) was added.

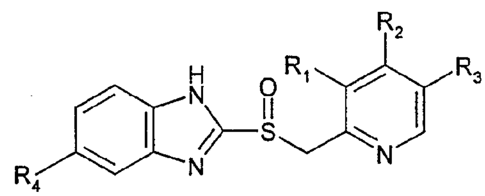
The mixture was stirred at 45-50°C for 20 hours. Further sodium perborate tetrahydrate (0.35 g) was added and the mixture was stirred at 45-50°C for a further 3 hours. A final batch of sodium perborate tetrahydrate (0.35 g) was added and the mixture stirred for a further 2 hours at 45-50°C. The mixture was cooled to 35°C and sodium hydrogen carbonate (4.9 g) was added followed by water (16.7 ml) and diisopropyl ether (16.2 ml). The mixture was stirred rapidly at 20-25°C for 1.5 hours. The mixture was filtered to give a product which was washed with water and dried under vacuum at 45-50°C to give 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphinyl}-1*H*-benzimidazole (6.5 g, 78.9% yield, purity by HPLC 95.5%).

Example 8

A mixture of 5-methoxy-2-mercapto-1H-benzimidazole (4.3 g), methanol (8.4 ml) and water (16.7 ml) was stirred while sodium hydroxide solution (4.7 ml, 46-48% w/w) was added over 5 minutes. The mixture was stirred at 45-50°C and a solution of 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (5.3 g) in water (25 ml) was added over 35 minutes at 45-50°C. The mixture was stirred at 45-50°C for 1.75 hours and then sodium perborate tetrahydrate (4.5 g) was added. The mixture was stirred at 45-50°C for 20 hours. Further sodium perborate tetrahydrate (0.35 g) was added and the mixture was stirred at 45-50°C for a further 3 hours. The mixture was cooled to 35°C and sodium hydrogen carbonate (4.9 g) was added followed by water (16.7 ml) and hexane (16.7 ml). The mixture was stirred rapidly at 20-25°C for 1.5 hours. The mixture was filtered to give a product which was washed with water and dried under vacuum at 45-50°C to give 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulphinyl}-1*H*-benzimidazole (6.6 g, 80.4% yield, purity by HPLC 94.45%).

CLAIMS

1. A process for the preparation a compound of formula I



I

in which R_1, R_2, R_3 and R_4 represent

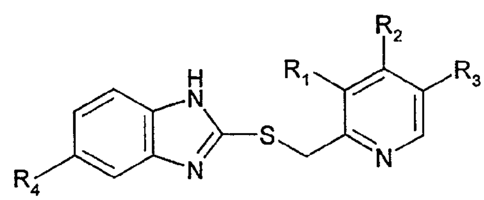
a) (R_1=CH_3; R_2=OCH_3; R_3=CH_3; R_4=OCH_3) or

b) (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) or

c) (R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) respectively

and pharmaceutically acceptable salts thereof

comprising reacting a compound of formula II



II

in which R_1, R_2, R_3 and R_4 represent

a) (R_1=CH_3; R_2=OCH_3; R_3=CH_3; R_4=OCH_3) or

b) (R_1=CH_3; R_2=OCH_2CF_3; R_3=H; R_4=H) or

c) (R_1=OCH_3; R_2=OCH_3; R_3=H and R_4=$OCHF_2$) respectively

with a perborate salt in a liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the liquid diluent employed.

2. A process as claimed in claim 1 wherein the perborate salt is sodium perborate.

3. A process as claimed in either claim 1 or claim 2 in which the amount of perborate salt employed in the process is in the range of 0.8 to 3 moles per mole of the compound of formula II employed in the process.

4. A process according to any previous claim in which the liquid diluent is selected from water, a C_{1-4} alcohol, toluene, tetrahydrofuran, acetone, a C_{2-6} diol, a C_{3-6} triol, ethyl acetate or mixtures thereof.

5. A process according to any previous claim in which the liquid diluent is a water/alcohol mixture.

6. A process according to any previous claim in which the process is carried out at a pH in the range of 8.5 to 12.

7. A process according to any previous claim in which a salt of the desired product is obtained.

8. A process according to any previous claim in which the compound of formula I is isolated as the free heterocycle.

9. A process according to any previous claim in which the process is carried out at a temperature in the range of 0 to 150°C.

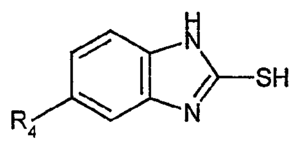
10. A process according to claim 1 in which a compound of formula IIa is reacted with sodium perborate in a mixture of water and methanol at a pH in the range of 8.5 to 10 at a temperature in the range of 15 -115°C to give a compound of formula Ia (omeprazole).

11. A process according to any previous claim wherein a purification solvent is added at the end of the oxidation reaction.

12. A process according to claim 11 wherein the purification solvent is a hydrocarbon or an ether.

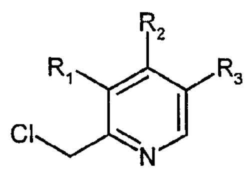
13. A process according to claim 12 wherein the purification solvent is selected from *tert*-butyl methyl ether or diisopropyl ether.

14. A process according to any previous claim in which the compound of formula II used is prepared by reacting a compound of formula III



III

or a salt thereof in which R_4 is as previously defined with a compound of formula IV



IV

or a salt thereof in which R_1, R_2, and R_3 are as previously defined, optionally in the presence of a base, in a second liquid diluent at a pH in the range of 7.5 to 14 at a temperature in the range of 0°C to the boiling point of the liquid diluent employed and is then reacted with a perborate salt without isolation.

15. A process according to claim 14 wherein the second liquid diluent is selected from water, a C_{1-4} alcohol, toluene, tetrahydrofuran, acetone, a C_{2-6} diol, a C_{3-6} triol, ethyl acetate or mixtures thereof.

16. A process according to claim 15 wherein the second liquid diluent is the same as the first.

17. A process according to any one of claims 14-16 wherein sodium hydroxide is used as the base.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	WO 99 02521 A (KAYANO AKIO ;NIIKAWA NOBUO (JP); EISAI CO LTD (JP); KURODA HIROFUM) 21 January 1999 see the whole document ---	1-17
X	FIESER,M.: "SODIUM PERBORAtE" REAGENTS FOR ORGANIC SYNTHESIS, vol. 12, 1986, page 452 XP002109649 NEW YORK see the whole document ---	1-17
X	PAQUETTE,L.A.: "SODIUM PERBORATE" ENCYCLOPEDIA OF REAGENTS FOR ORGANIC SYNTHESIS, vol. 7, 1995, pages 4611-4613, XP002109650 CHICHESTER see the whole document --- -/--	1-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1999	06/08/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 91 19712 A (ASTRA AB) 26 December 1991 see the whole document ---	1-17
Y	EP 0 197 013 A (HAESSLE AB) 8 October 1986 see the whole document ---	1-17
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 197 (C-0833), 21 May 1991 & JP 03 052887 A (YOSHITOMI PHARMACEUT IND LTD), 7 March 1991 see abstract ---	1-17
Y	EP 0 484 265 A (GENESIS PARA LA INVESTIGACION ;ESTEVE QUIMICA SA (ES)) 6 May 1992 see the whole document -----	1-17

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